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An overview of angioedema: Clinical features, diagnosis, and management

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INTRODUCTION — Angioedema is self-limited, localized subcutaneous (or submucosal) swelling, which results from extravasation of fluid into interstitial tissues. Angioedema may occur in isolation, accompanied by urticaria, or as a component of anaphylaxis.

The clinical features, diagnosis, differential diagnosis, and management of angioedema will be reviewed here. The pathogenesis and causes of angioedema are discussed separately. (See "An overview of angioedema: Pathogenesis and causes".)

CLINICAL FEATURES — Angioedema typically affects areas with loose connective tissue, such as the face, lips, mouth, and throat, larynx, uvula, extremities, and genitalia. Bowel wall angioedema presents as colicky abdominal pain.

Angioedema can be distinguished clinically from other forms of edema by the following characteristics:

- Onset in minutes to hours
- Asymmetric distribution
- Tendency not to involve gravitationally dependent areas
- Involvement of face, lips, larynx, and bowels
- Association of some forms of angioedema with other signs and symptoms of allergic reactions or anaphylaxis

Types of angioedema — Two types of angioedema can be distinguished: mast cell-mediated angioedema and bradykinin-mediated angioedema. However, for many of the known triggers of angioedema, the mechanism is unclear. (See "An overview of angioedema: Pathogenesis and causes".)

- In mast cell-mediated angioedema, such as allergic reactions to foods or insect

stings, there are often (not always) other signs and symptoms of mast cell mediator release. These signs and symptoms include urticaria, flushing, generalized pruritus, bronchospasm, throat tightness, and/or hypotension. Mast cell-mediated angioedema usually begins within minutes of exposure to the allergen, builds over a few hours, and resolves in 24 to 48 hours. (See "An overview of angioedema: Pathogenesis and causes", section on 'Mast cell-mediated etiologies'.)

- Bradykinin-induced angioedema is not associated with urticaria, bronchospasm, or other symptoms of allergic reactions. It has a somewhat more prolonged timecourse, usually developing over 24 to 36 hours and resolving within two to four days [1]. In this type of angioedema, the relationship between the trigger and the onset of symptoms is often not apparent. As an example, in ACE inhibitor-induced angioedema, swelling may appear within a week of starting or increasing the medications, or after years of use. (See "An overview of angioedema: Pathogenesis and causes", section on 'Bradykinin-mediated etiologies'.)

Anatomic sites

Larynx — Laryngeal edema can develop rapidly (over minutes) or more slowly over several hours. Early symptoms include hoarse voice, throat tightness, and difficulty swallowing. Assessment and treatment are discussed below (see 'Angioedema in or near the airway' below).

Skin and mucous membranes — Angioedema affects the subcutaneous and submucosal tissues (picture 1 and picture 2 and picture 3). Pruritus is absent, unless the angioedema is associated with urticarial lesions, which are intensely pruritic (picture 4). The skin is either normal in color or mildly erythematous. Mild pain and warmth may be present, but are much less prominent than the pain and warmth of cellulitis. Some patients describe the discomfort of angioedema as burning in nature. Angioedema resolves without leaving residual markings on the skin, unless there has been trauma induced by rubbing or scratching.

Bowel wall — Angioedema affecting the bowel wall presents as colicky abdominal pain, sometimes accompanied by vomiting and/or diarrhea. Bowel wall edema can often be visualized by abdominal CT or ultrasound.

Bowel wall angioedema is seen in patients on ACE inhibitors and in those with hereditary or acquired C1 inhibitor deficiency. A more detailed discussion of the evaluation of abdominal pain in patients with hereditary angioedema is found separately. (See "Clinical manifestations and pathogenesis of hereditary angioedema", section on 'Abdominal attacks'.)

Life-threatening situations — Angioedema is usually a benign condition, although it can be life-threatening in the following situations:

- Angioedema of the larynx, upper airway, or tongue (of any mechanism) can progress to airway obstruction and asphyxiation.

- Angioedema may be a presenting symptom of anaphylaxis (a serious allergic reaction that is rapid in onset and may cause death). The diagnosis and treatment of anaphylaxis are presented separately. (See "Anaphylaxis: Rapid recognition and treatment".)

DIAGNOSTIC EVALUATION — In patients presenting with angioedema affecting the airway, airway protection must be given priority over a comprehensive diagnostic evaluation. (See 'Angioedema in or near the airway' below.)

Clinical history — The history should be directed at identifying possible causes, as well as determining if the patient has had previous episodes of angioedema. Causes are reviewed elsewhere. (See "An overview of angioedema: Pathogenesis and causes".)

- The patient should be questioned about any unusual exposures (eg, insect stings), activities (eg, exercise), foods or other ingestions in the 24 hours before the onset of symptoms.

- A review of the patient's medications is important, with particular attention to the following:

  - Nonsteroidal antiinflammatory drugs (NSAIDs)
  - ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)
  - Calcium channel blockers
  - Estrogens
  - Fibrinolytic agents
  - Any new medications or significant increases in doses of medications

- Patients with previous episodes of angioedema (cutaneous swelling or abdominal pain) should be asked about activities and exposures surrounding those episodes, to see if any pattern is apparent. Individuals with ACEI-induced angioedema may have several episodes of swelling before the drug is recognized as the culprit and discontinued [2]. Patients with recurrent orofacial angioedema after dental work or episodes of unexplained abdominal pain may have hereditary or acquired C1 inhibitor deficiency.

- Patients should be asked about family members with similar episodes of cutaneous or laryngeal angioedema or with recurrent abdominal pain, to identify

families with hereditary angioedema (HAE). However, about 25 percent of patients with HAE have a new mutation and so do not have a positive family history. (See "Clinical manifestations and pathogenesis of hereditary angioedema".)

Physical examination — The presence of other signs and symptoms of an allergic reaction (or more precisely, of mast cell activation) is helpful in narrowing the list of possible causes, as mentioned previously. These signs and symptoms include urticaria, flushing, generalized pruritus, bronchospasm, throat tightness, and/or hypotension. If one or more of these other signs or symptoms are present, the history should be directed toward mast cell-mediated etiologies, such as allergic reactions to foods, drugs, and stinging insects (table 1) [3]. (See "An overview of angioedema: Pathogenesis and causes", section on 'Mast cell-mediated etiologies'.)

If signs and symptoms of mast cell activation are absent, then bradykinin-mediated angioedema, such as that caused by ACE inhibitors and the rare disorders hereditary or acquired C1 inhibitor deficiency, should be considered. (See "An overview of angioedema: Pathogenesis and causes", section on 'Bradykinin-mediated etiologies'.)

Laboratory tests — The laboratory tests that are indicated in a patient presenting with angioedema are influenced by the presence of other signs and symptoms and by the suspected cause, as described below. However, we suggest that the following laboratories be considered in all patients with new-onset angioedema: complete blood count with differential, basic chemistry panel with liver function tests, C4 and C3 levels. Depressed C4 levels should prompt further evaluation for complement mediated angioedema, and low levels C3 and C4 levels suggest an immune complex mediated process, such as systemic lupus erythematosus. (See 'Differential diagnosis' below.)

Angioedema with prominent urticaria — Guidelines for the evaluation of urticaria (with or without angioedema) suggest that the following tests be obtained: a complete blood count with differential, urinalysis, erythrocyte sedimentation rate, and liver function tests [4]. This evaluation is reviewed separately. A specific cause can sometimes be identified in patients with new onset urticaria/angioedema. (See "New onset urticaria: Diagnosis and treatment" and "New onset urticaria: Epidemiology, clinical manifestations, and etiologies".)

Urticaria/angioedema is considered chronic when it has been present on most days of the week for a period of six weeks or more. The evaluation of chronic urticaria/angioedema differs from that of new-onset symptoms, since a specific external trigger or allergy is not found in most patients and laboratory studies are most often normal. (See "Chronic urticaria: Diagnosis, theories of pathogenesis, and natural history".)

Angioedema with anaphylaxis — A serum total tryptase level drawn shortly after the onset of anaphylaxis may be useful in confirming that the episode was a mast cell-mediated event. Serum tryptase is a mast cell-specific protease that is released upon mast cell activation. Any elevation in serum tryptase suggests an anaphylactic event. However, a normal level does not exclude anaphylaxis because tryptase elevations are variable and transient. Typtase elevations are most consistently found in patients with hypotension during anaphylaxis. Instruction for proper sample collection are provided in the table (table 2). (See "Laboratory tests to support the clinical diagnosis of anaphylaxis".)

Angioedema due to a suspect allergen — In cases in which an allergic reaction to an identifiable allergen, such as a food or an insect sting, is suspected, there may be commercially-available tests for IgE antibodies to the allergen in question. Allergen-specific IgE immunoassays are available for a variety of foods, insect venoms, inhaled allergens, and latex. These tests vary in sensitivity and specificity, but a positive result can be helpful. IgE immunoassays are not altered by recent allergic reactions, so they can be obtained at any time. Allergy skin testing provides similar information and is more sensitive in many cases, but it requires referral to an allergy specialist and should be deferred until the patient has fully recovered. (See "Overview of in vitro allergy tests", section on 'Immunoassays' and "Overview of skin testing for allergic disease".)

Patients taking an ACE inhibitor or ARB — Some experts have advised screening for underlying defects in C1 inhibitor with a serum C4 level [5].

Isolated angioedema — Screening tests for C1 inhibitor deficiency should be obtained in patients with isolated mucosal or cutaneous angioedema (ie, without urticaria or other evidence of mast cell involvement) or bowel wall angioedema on imaging of the abdomen [6]. The recommended tests are:

- C4 level
- C1 inhibitor (antigenic level)

The evaluation and diagnosis of C1 inhibitor deficiency are reviewed in more detail separately. (See "Diagnosis of hereditary angioedema" and "Acquired C1 inhibitor deficiency: Diagnosis, management, and prognosis".)

Diagnosis — The diagnosis of angioedema is made clinically, based on a suggestive history and physical findings. Laboratories may be helpful in confirming

an underlying allergy or a complement disorder. However, laboratories are normal in many cases of angioedema.

Extensive empiric testing — Extensive testing beyond the laboratory tests already mentioned is of relatively low yield. (See 'Laboratory tests' above.)

The utility of extensive testing was evaluated in a large series of 776 patients with recurrent angioedema, without major urticaria, who presented to a referral center over a 10 year period [7]. In the majority of these patients, angioedema was not associated with an obvious trigger. All patients underwent a careful history and physical examination, sinus and dental radiographs, complete blood count, serum protein electrophoresis, complement studies, erythrocyte sedimentation rate, C-reactive protein, hepatic enzymes, renal function, thyroid function and anti-tissue antibodies, stool examination for ova and parasites, urinalysis, pharyngeal cultures, and urine cultures. Further studies, including allergy testing or medication withdrawal and challenge, were performed if allergy was suggested by the clinical history. A condition or trigger was considered causative only if the angioedema improved after treatment/discontinuation.

The following potentially causative conditions were identified (figure 1):

- Hereditary and acquired angioedema was identified in 23 and 2 percent, respectively.
- ACE inhibitors were implicated in 11 percent, with a median duration of treatment of one year before symptoms began.
- Other disorders, most commonly chronic infection or autoimmune disease, were identified in 7 percent.
- Three percent did not have angioedema, but rather other types of peripheral or generalized edema. (See 'Differential diagnosis' below.)

No trigger could be identified in 38 percent, and these patients were deemed to have idiopathic angioedema. If complement studies had been done and ACE inhibitors discontinued prior to referral, as suggested in the approach described in this topic review, then a causative condition would have been found in just 7 percent of these referred patients [7].

Idiopathic angioedema — Idiopathic angioedema is the term applied to recurrent episodes of angioedema without urticaria, for which no explanation can be found after a thorough evaluation (as previously described) to exclude allergic disorders, drug reactions, and defects in complement pathways [7].

DIFFERENTIAL DIAGNOSIS — There are several conditions that may be mistaken for angioedema [5,8].

Disorders resembling cutaneous edema — Cutaneous edema mimicking angioedema can result from contact dermatitis, cellulitis, autoimmune diseases, superior vena cava syndrome, and other disorders.

- Contact dermatitis — Contact dermatitis is a common mimic of facial angioedema and can cause dramatic swelling of the facial and periorbital skin when it develops in response to cosmetics or topical pharmaceuticals (picture 5 and picture 6). Microvesiculation and/or deep erythema of the skin can help distinguish contact dermatitis from complement-mediated angioedema. Poison ivy can cause severe facial swelling, although linear patterns of vesiculations are often present.

Patients with contact dermatitis often report prominent pain and burning of the skin. Resolution of contact dermatitis may be followed by peeling, which does not occur in angioedema. (See "Overview of dermatitis" and "Contact dermatitis in children".)

- Cellulitis and erysipelas — Cellulitis and erysipelas are infections of various layers of the dermis, which present as areas of skin erythema, edema and warmth in the absence of an underlying suppurative focus. Cellulitis involves the deeper dermis and subcutaneous fat and has relatively smooth, flat borders. In contrast, erysipelas involves the upper dermis and superficial lymphatics and is characteristically raised above the level of surrounding skin, with a clear line of demarcation between involved and uninvolved tissue (picture 7 and picture 8).

Compared with angioedema, cellulitis and erysipelas are deeply erythematous, painful, and may be accompanied by fever. The involved areas of skin are more clearly demarcated than angioedematous skin. Resolution may be followed by peeling, whereas angioedema resolves without peeling.

- Facial lymphedema — Facial lymphedema can be associated with rosacea, although there are other characteristic skin changes in rosacea. Patients may also experience prominent flushing and warmth of the face, and the combination of flushing, heat, and swelling is interpreted by some patients as a possible allergic reaction. However, lymphedema does not develop or resolve rapidly, in contrast to angioedema. (See "Rosacea".)

- Autoimmune conditions — Edema of the face, periorbital areas, and sometimes

the hands can be seen in systemic lupus, polymyositis, dermatomyositis, and Sjogren's syndrome. Early stages of both scleredema and systemic sclerosis can present as swelling. Scleredema often involves the posterior neck, and systemic sclerosis often affects the hands and is accompanied by Raynaud's phenomenon [9]. These disorders can be distinguished from angioedema by the presence of associated systemic rheumatologic findings. (See "Diagnosis and differential diagnosis of systemic sclerosis (scleroderma) in adults".)

- Eyelid edema — Blepharochalasis is an uncommon disorder in which recurrent and episodic eyelid edema leads to atrophic eyelid skin with fine wrinkling and bronze discoloration [4,10,11]. This is seen predominantly in children and young adults. The etiology is unknown, although IgA deposits have been described in the periorbital tissues, suggesting an immunological pathogenesis [12].

- Parasitic infections — In areas of the world where parasitic infections are prevalent, certain infections can cause periorbital edema that is persistent rather than episodic. Specific infections that can present with this finding include trichinosis and American trypanosomiasis (ie, Romana's sign) [13]. (See "Trichinellosis" and "Pathology and pathogenesis of Chagas disease", section on 'Acute phase'.)

- Hypothyroidism — Severe hypothyroidism can cause a puffiness of the face and lips that can be mistaken for angioedema, but is not transient. Nonpitting edema (myxedema) may be generalized. Myxedema results from infiltration of the skin by glycosaminoglycans with associated water retention. (See "Clinical manifestations of hypothyroidism".)

- Hyperthyroidism — Hyperthyroidism due to Graves disease can also include an infiltrative dermopathy, usually of the skin overlying the shins, where it presents as raised, hyperpigmented, violaceous, orange-peel textured papules. (See "Pretibial myxedema in autoimmune thyroid disease".)

- Superior vena cava syndrome and tumors — Occasionally, edema of the face, neck, or upper extremities, accompanied by venous engorgement, is observed with superior vena cava syndrome [13]. (See "Malignancy-related superior vena cava syndrome".) Tumors of the head and neck and lymphoma can also cause localized edema. With these entities, protracted or progressive swelling would be expected, in contrast to the transient swelling of angioedema.

- Cheilitis granulomatosa (Miescher's cheilitis) and Melkersson-Rosenthal syndrome — These are rare disorders of recurrent angioedema involving the lips and face that lead to eventual permanent enlargement of the affected areas (picture 9 and picture 10) [14,15].

- Idiopathic edema — Idiopathic edema (as opposed to idiopathic angioedema) is a syndrome of persistent and recurrent fluid retention, typically occurring in young, menstruating women in the absence of cardiac, hepatic, or renal disease. (See "Idiopathic edema".)

Disorders resembling laryngeal edema — The differential diagnosis of laryngeal edema includes tonsillitis, peritonsillar abscess, and pharyngeal foreign body [5]. Historical information should differentiate these entities from angioedema, as infectious causes should have accompanying fever and other signs of illness. The diagnosis of a pharyngeal foreign body can be difficult, however, particularly in the preverbal infant. (See "Emergent evaluation of acute upper airway obstruction in children".)

Other causes of bowel wall edema — Thickening of the wall of the small bowel can be seen in multiple disorders, including mesenteric infarction, inflammatory bowel disease, acute ileitis (Yersinia, Campylobacter infections), peritoneal carcinomatosis, inflammatory conditions adjacent to the bowel wall, and other disorders [16,17].

TREATMENT — The treatment of angioedema depends upon the acuity, severity, and proposed mechanism.

Angioedema in or near the airway — The patient with angioedema near or involving the tongue, uvula, soft palate, or larynx must be immediately assessed for signs of airway compromise. The airway should be managed by the most experienced person available, as intubation in the presence of laryngeal angioedema can be difficult due to distortion of the normal anatomy. Angioedema sometimes spreads to adjacent areas, and frequent monitoring of airway patency is critical throughout treatment. (See "The difficult airway in adults" and "The difficult pediatric airway".)

Angioedema in anaphylaxis — Anaphylaxis should be treated with intramuscular epinephrine, intravenous fluids, and oxygen. Rapid overview tables are provided for treatment of anaphylaxis in adults (table 3) and children (table 4). The treatment of anaphylaxis is reviewed in greater detail elsewhere. (See "Anaphylaxis: Rapid recognition and treatment".)

All patients who have experienced anaphylaxis should be equipped with an anaphylaxis emergency action plan, one or more epinephrine auto-injectors, a plan for arranging further evaluation, and printed information about anaphylaxis and its treatment. These materials can be found separately. (See "Anaphylaxis: Rapid recognition and treatment", section on 'Discharge care'.)

Acute allergic angioedema (less severe than anaphylaxis) — Antihistamines

and glucocorticoids are the main therapies, for isolated angioedema appears to be allergic (ie, mast-cell mediated) but is NOT part of a larger anaphylactic reaction (since anaphylaxis is treated with intramuscular epinephrine). This approach is extrapolated from the treatment of acute urticaria/angioedema, as the data on isolated allergic angioedema are scant [5]. (See "New onset urticaria: Diagnosis and treatment", section on 'Treatment'.)

Summarized briefly here, suggested treatment includes the following:

- H1 and H2 antihistamines at standard doses.
- Prednisone (20 to 40 mg daily) in adults or prednisolone (0.5 to 1 mg/kg/day) in children, tapered over five to seven days.

Antihistamines and glucocorticoids will likely be ineffective if the angioedema is bradykinin-mediated.

C1-inhibitor deficiency (hereditary angioedema) — The treatment of acute attacks of hereditary and acquired C1 inhibitor disorders is outlined here and discussed in detail separately.

The treatment of laryngeal attacks, which are the leading cause of mortality in patients with hereditary angioedema, must always begin with immediate and meticulous attention to airway patency, regardless of the therapies available. (See 'Angioedema in or near the airway' above.) Those with respiratory distress or stridor may require intubation, because even the first line therapies take approximately 30 minutes or more to begin working.

Briefly, treatment options include:

- Purified C1 inhibitor concentrate (Cinryze®, Berinert®)
- Ecallantide (Kalbitor®) (a kallikrein inhibitor available in the United States)
- Fresh frozen plasma (used in the US) or solvent-detergent treated plasma (used in the European Union [EU])

In the EU, another option is icatibant (Firazyr®), a bradykinin B2 receptor antagonist that is not available in the US.

The dosing and administration of each of these therapies is reviewed separately. (See "Treatment of acute attacks in hereditary angioedema", section on 'Medication options' and "Acquired C1 inhibitor deficiency: Diagnosis, management, and prognosis".)

ACE inhibitor- and ARB-induced angioedema — Treatment of ACEI-induced angioedema primarily involves discontinuation of the drug. The airway must be protected, as several deaths have been attributed to asphyxiation in the setting of

massive tongue swelling [18]. Symptoms usually resolve within 24 to 48 hours [19]. The pathogenesis and incidence of ACE inhibitor and ARB-induced angioedema are discussed separately. (See "An overview of angioedema: Pathogenesis and causes", section on 'Bradykinin-mediated etiologies'.)

The utility of other medications (including antihistamines, glucocorticoids, and epinephrine) in the treatment of ACEI-induced angioedema has not been reported.

Treatment of refractory symptoms — Case reports describe successful treatment of fresh frozen plasma in life-threatening ACE inhibitor-induced angioedema [19,20]. C1-inhibitor concentrate has also been administered in this situation [21,22]. Ecallantide and icatibant have not been studied in the treatment of ACE inhibitor and ARB-induced angioedema, but these drugs should theoretically be useful and may be options in the future. The dosing and administration of each of these therapies is reviewed separately. (See "Treatment of acute attacks in hereditary angioedema", section on 'Medication options'.)

Patients should be advised to obtain a medical identification bracelet or tag listing their sensitivity to the culprit class of medication.

Recurrent, idiopathic angioedema — A trial of nonsedating antihistamines, administered twice daily, is suggested as an initial therapeutic intervention in patients with idiopathic recurrent angioedema without urticaria.

In the largest series available, 294 patients with idiopathic recurrent angioedema without urticaria were treated with nonsedating antihistamines initially (ie, either cetirizine 10 mg twice daily or desloratadine 5 mg twice daily) for at least one month [7]. With this intervention, 86 percent experienced significant improvement or resolution of the angioedema. In those that did not improve significantly (40 patients), the addition of hydroxyzine (25 mg three times daily) did not result in additional symptom control. Responsiveness to antihistamines suggests that mast-cell or basophil-mediated processes were underlying the symptoms of these patients, despite the lack of identifiable triggers.

For adult patients with idiopathic angioedema who have infrequent attacks (ie, a few attacks per year) and do not wish to take regular medications for prevention, we (the authors and editors of UpToDate) have found the following to be helpful. We instruct patients to take 40 mg of prednisone and 25 to 50 mg of diphenhydramine, all at once, at the first sign of swelling, with no further doses. Some patients have identifiable sensations in the skin just before the onset of angioedema, and the medications should be taken when these sensations appear. This approach has not been formally studied.

REFERRAL — Patients with severe or recurrent angioedema or angioedema/urticaria, for which no cause is readily apparent, should be referred to

a specialist for further evaluation. An allergy specialist is most appropriate if an allergic cause or C1 inhibitor deficiency is suspected. Other allergy and dermatology specialists manage mast cell-mediated urticaria/angioedema.

SUMMARY AND RECOMMENDATIONS

- Angioedema typically affects the skin and mucosal tissues of the face, lips, mouth, and throat, larynx, extremities, and genitalia, often in an asymmetric pattern (picture 1). Angioedema can also affect the bowel wall and present as colicky abdominal pain. (See 'Clinical features' above.)

- Two types of angioedema can be distinguished: mast cell-mediated angioedema (eg, allergic reactions) and bradykinin-mediated angioedema (eg, ACE inhibitor induced angioedema, hereditary angioedema). However, there are other causes of angioedema for which the mechanism unknown. (See "An overview of angioedema: Pathogenesis and causes".)

- Angioedema may be life-threatening if it causes airway obstruction or when it represents a component of anaphylaxis. (See 'Life-threatening situations' above.)

- If the clinical history or physical exam reveals a possible external cause or concomitant condition, then these findings should guide further testing. If there is no information to suggest an external cause and the patient has isolated angioedema (without pruritus or urticaria), then a C4 and a C1 inhibitor antigenic level should be obtained. (See 'Diagnostic evaluation' above.)

- Immediate assessment and ongoing protection of the airway is critical in any patient with angioedema near or affecting the larynx, mouth, soft palate, or tongue. (See 'Angioedema in or near the airway' above.)

- The treatment of angioedema depends upon the acuity, severity, and the mechanism believed responsible (mast cell or bradykinin-mediated). Mast cell-mediated angioedema responds to epinephrine (if severe), glucocorticoids, and antihistamines. In contrast, bradykinin-mediated angioedema responds to C1-inhibitor concentrate, fresh frozen plasma, and other agents that interfere with the production or action of bradykinin. (See 'Treatment' above.)

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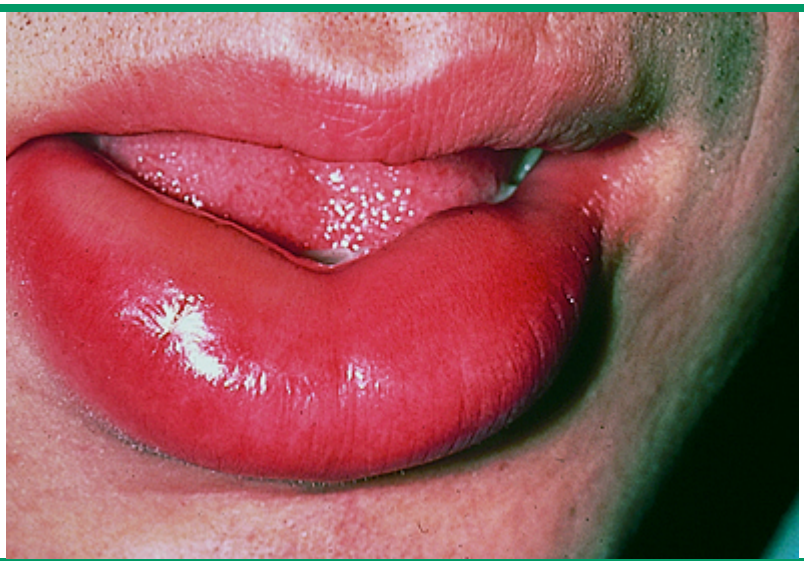
GRAPHICS

Angioedema lip



Angioedema is a diffuse, nonpitting, tense swelling of the dermis and subcutaneous tissue. It develops over minutes to hours, and resolves over subsequent hours or days. Angioedema typically does not itch, unless it is associated with urticaria.

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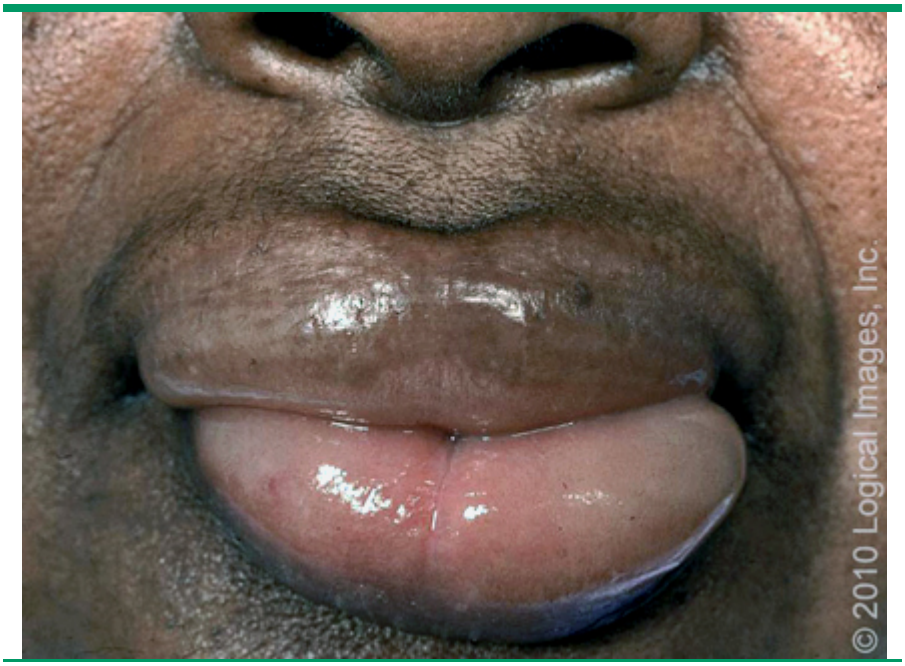
Angioedema of the lower lip



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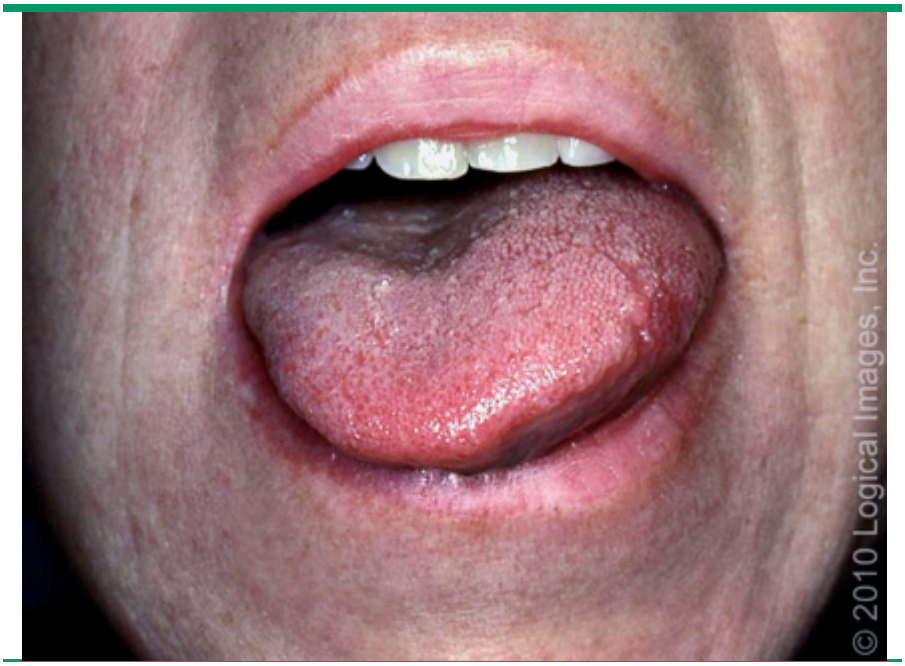
Unilateral angioedema of the tongue



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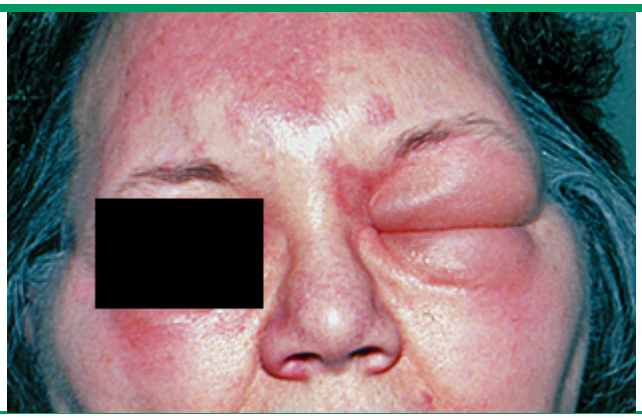
Angioedema and hives face



Facial angioedema and urticaria (forehead).

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Major causes of mast cell-mediated angioedema

IgE-dependent allergic reactions
Foods
Drugs (antibiotics, local anesthetics, hormones)
Stinging insects
Latex
Contact (fresh fruits and vegetables, animal saliva)
Direct mast cell mediator release
Opiates
Muscle relaxants (succinylcholine, curare)
Radiocontrast agents
Perturbations in arachidonic acid metabolism within mast cells
Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs)

Instructions for optimal collection and handling of blood samples for measurement of tryptase and histamine following suspected anaphylaxis

Tryptase (serum or plasma)

When to collect the sample:

Blood should be collected within the first one to three hours after symptom onset whenever possible; samples collected <15 min or >4 h after symptom onset are less likely to be informative.

How to collect the sample:

Blood can be drawn using normal technique. Collect blood for serum (red top tube) or plasma (tube with heparin, citrate or EDTA). A minimum of 1 mL is required.

For postmortem samples, blood is best collected from the femoral artery or vein.

How to process the sample:

Serum or plasma should be placed on ice and frozen as soon as possible. Samples should be shipped frozen by overnight courier if the assay cannot be performed on site.

Histamine (plasma)

When to collect the sample:

Plasma for histamine levels should be collected as soon as possible after symptom onset: preferably within 15 min; samples collected >30 min after symptom onset are less likely to be informative.

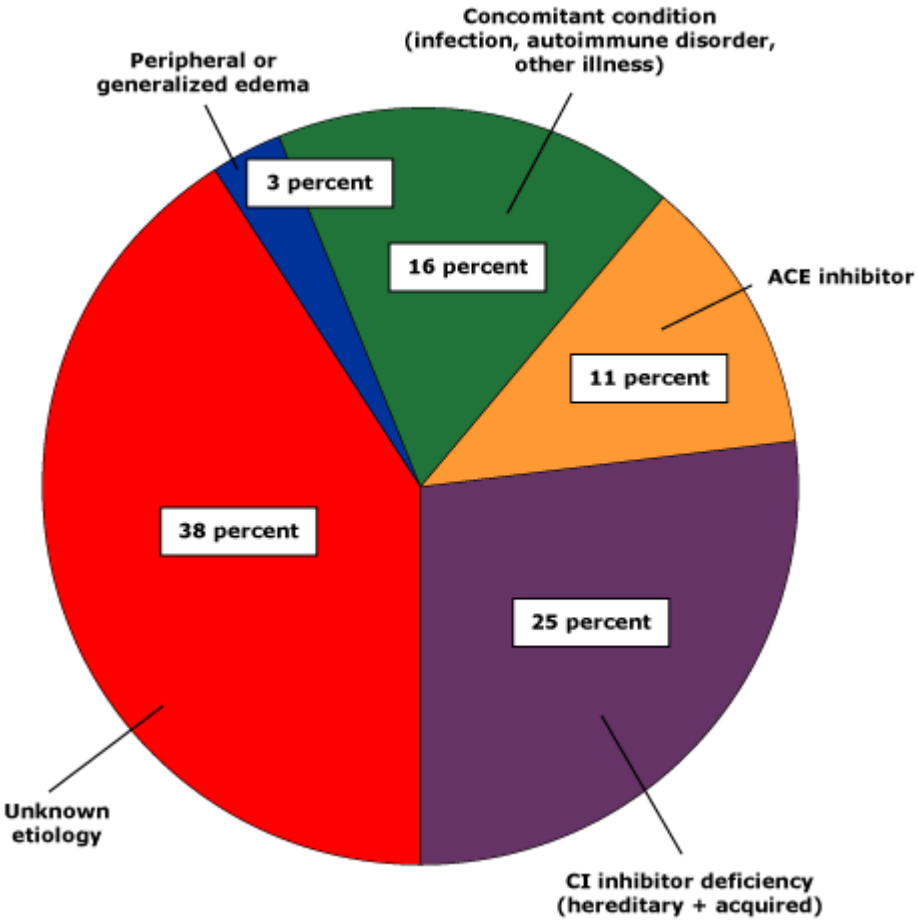
How to collect the sample:

Pull blood manually (DO NOT use vacuum tubes) under gentle pressure through a 20 gauge or larger needle into a syringe containing either citrate or EDTA.

How to process the sample:

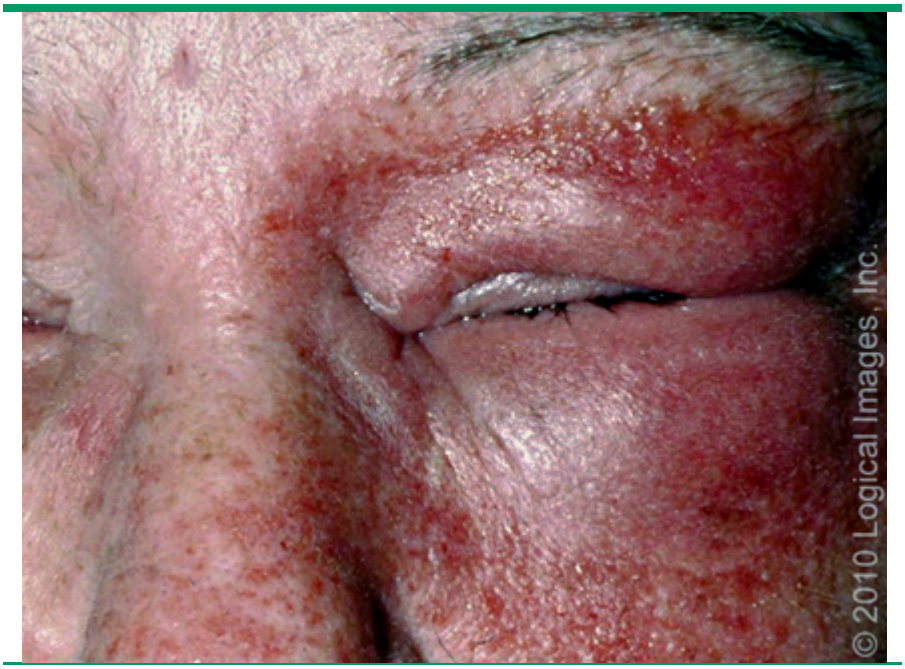
Anticoagulated blood should be placed on ice and centrifuged to separate plasma from cells as soon as possible, and then frozen until ready to be analyzed.

Etiologies of angioedema in referral populations



Data from: Zingale, LC, Beltrami, L, Zanichelli, A, et al. Angioedema without urticaria: a large clinical survey. CMAJ 2006; 175:1065.

Contact dermatitis of the periorbital skin



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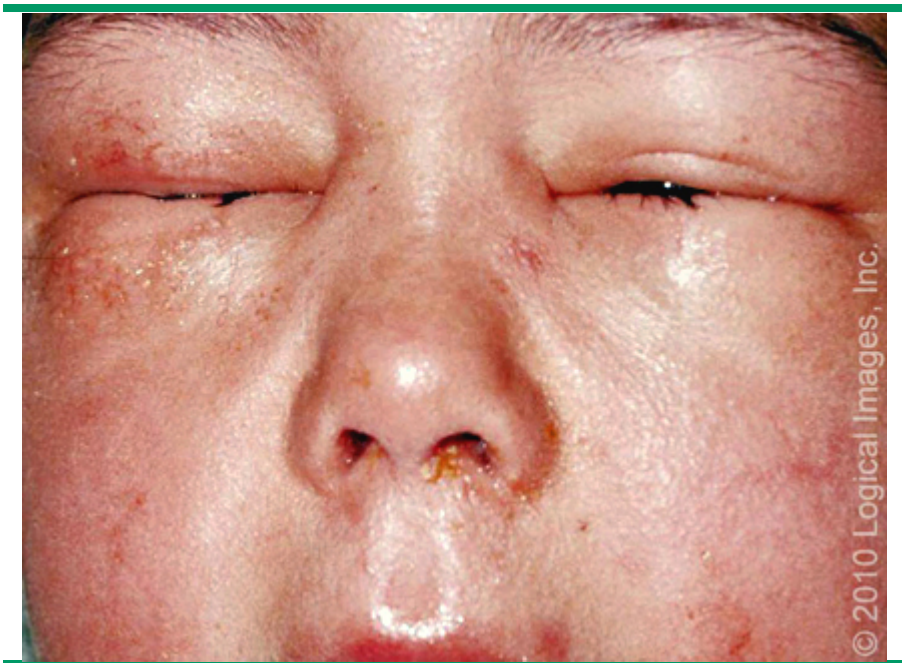
Contact dermatitis involving the facial and periorbital skin



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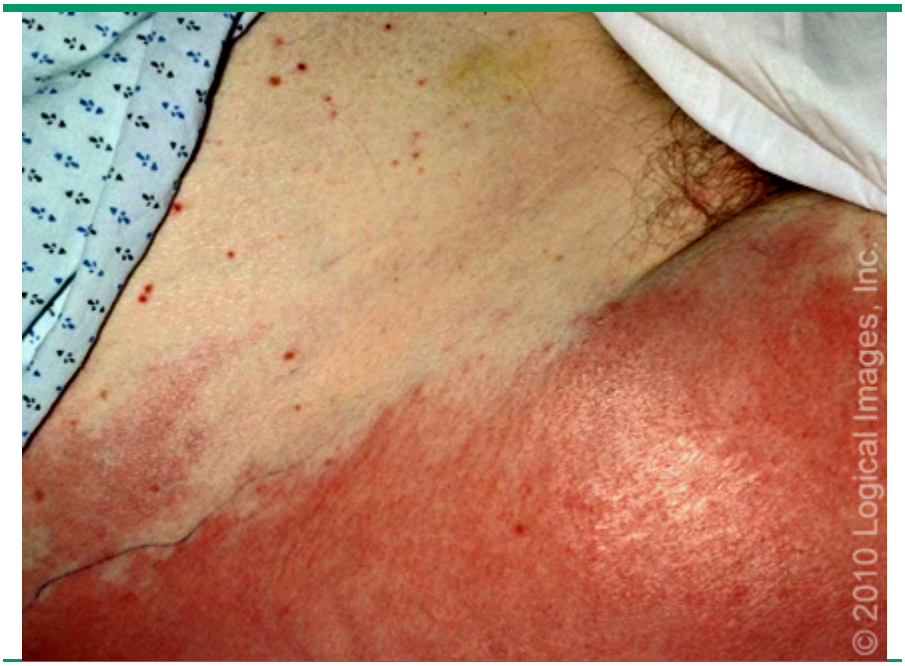
Erysipelas involving the groin and thigh



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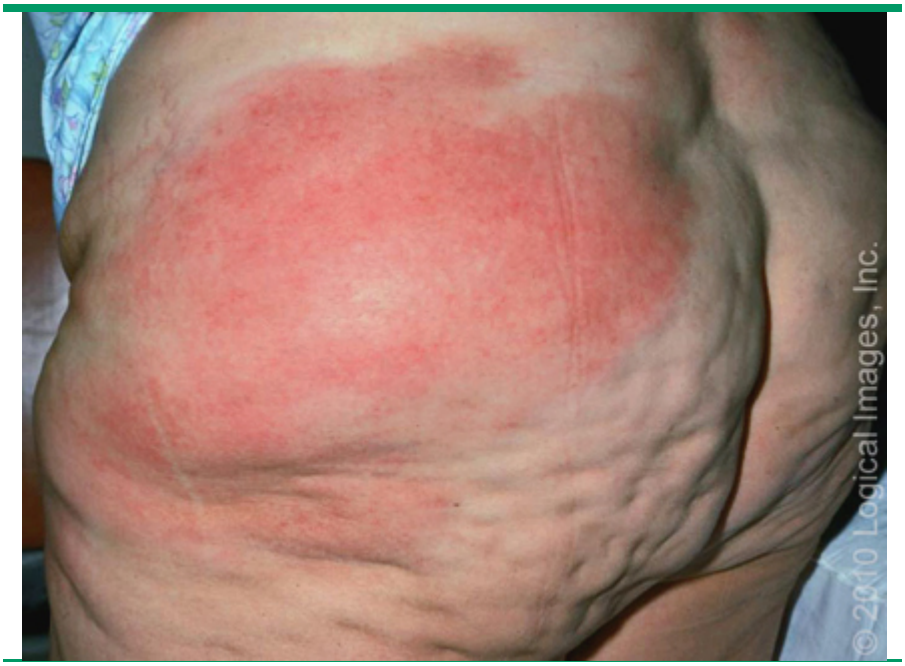
Erysipelas involving the buttock



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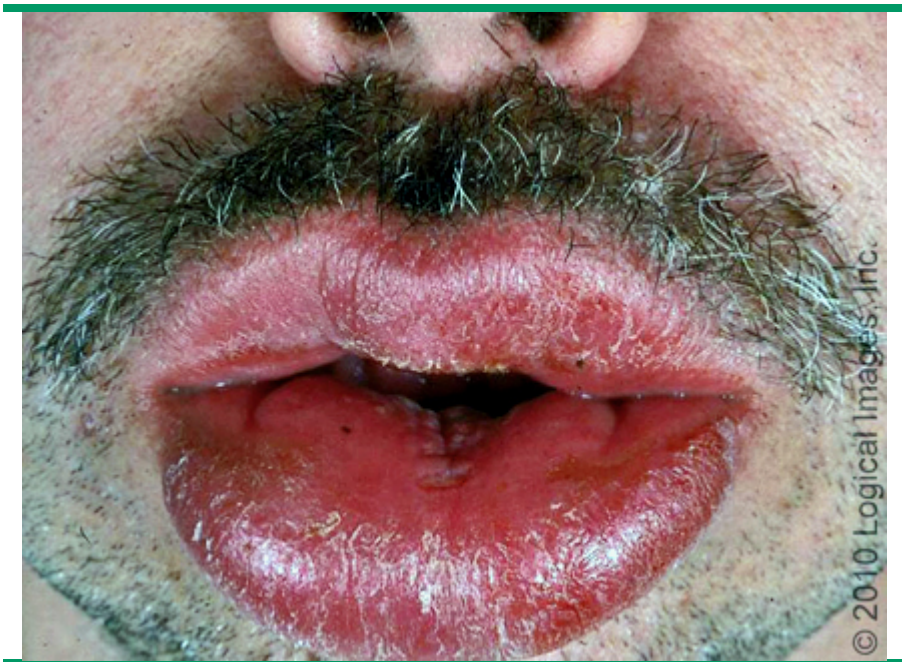
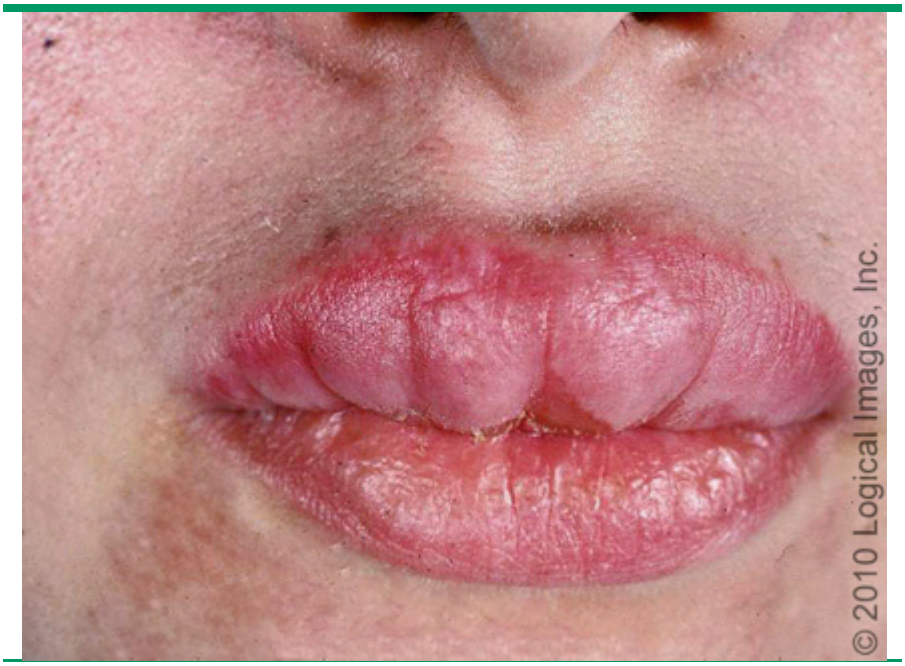
Granulomatous cheilitis



Granulomatous cheilitis is a rare disorder in which recurrent swelling of the lips leads to permanent areas of enlargement. *Reproduced with permission from: www.visualdx.com. Copyright Logical Images, Inc.*

Granulomatous cheilitis



Granulomatous cheilitis is a rare disorder in which recurrent swelling of the lips leads to permanent areas of enlargement. *Reproduced with permission from: www.visualdx.com. Copyright Logical Images, Inc.*

Rapid overview: Emergent management of anaphylaxis in adults

DIAGNOSIS IS MADE CLINICALLY:
Most common signs and symptoms are cutaneous (eg, urticaria, angioedema, flushing, pruritus). However, some patients have no skin findings.
Danger signs: Rapid progression of symptoms, respiratory distress (eg, wheezing, increased work of breathing, persistent cough, stridor), persistent vomiting, hypotension, dysrhythmia, chest pain, syncope
ACUTE MANAGEMENT:
The first and most important therapy in anaphylaxis is epinephrine. There are **NO absolute contraindications** to epinephrine in the setting of anaphylaxis.
Airway: Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult; cricothyrotomy may be necessary
Promptly and simultaneously, give:
IM Epinephrine (1 mg/mL preparation): Give aqueous epinephrine 0.3 to 0.5 mg intramuscularly, preferably in the mid-anterolateral thigh; can repeat every 3 to 5 minutes as needed. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below).
Place patient in recumbent position, if tolerated, and elevate lower extremities
Oxygen: Give 6 to 8 liters per minute via face mask, or up to 100 percent oxygen as needed
Normal saline rapid bolus: Treat hypotension with rapid infusion of 1 to 2 liters IV; repeat as needed; massive fluid shifts with severe loss of intravascular volume can occur
Also consider administration of:
Albuterol: For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer; repeat as needed
H1 antihistamine: Give diphenhydramine 25 to 50 mg IV (for relief of urticaria and itching only)
H2 antihistamine: Consider giving ranitidine 50 mg IV
Glucocorticoid: Consider giving methylprednisolone 125 mg IV

Continuous non-invasive hemodynamic and pulse oximetry monitoring should be performed
TREATMENT OF REFRACTORY SYMPTOMS:
Epinephrine infusion: For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, 2 to 10 micrograms per minute by infusion pump. Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation, as assessed by continuous non-invasive monitoring.
Vasopressors: Patients may require vasopressors, given by infusion pump, with the doses titrated continuously according to blood pressure, cardiac rate and function, and oxygenation, as assessed by continuous non-invasive monitoring
Glucagon: Patients on beta-blockers may not respond to epinephrine and can be given glucagon 1 to 2 mg IV over 5 minutes, followed by infusion of 5 to 15 micrograms per minute

Rapid Overview: Emergent management of anaphylaxis in infants and children

DIAGNOSIS IS MADE CLINICALLY
Most common signs and symptoms: cutaneous (eg, urticaria, angioedema, flushing, pruritus) and vomiting
Danger signs: Rapid progression of symptoms, evidence of respiratory distress (eg wheezing, increased work of breathing, retractions, persistent cough, stridor), signs of poor perfusion*, dysrhythmia, syncope
ACUTE MANAGEMENT
The first and most important therapy in anaphylaxis is epinephrine. There are **no absolute contraindications** to epinephrine in the setting of anaphylaxis
Airway: Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult and cricothyrotomy may be necessary
IM Epinephrine (1 mg/mL preparation): Give epinephrine 0.01 mg per kilogram intramuscularly (maximum per dose: 0.5 mg), preferably in the mid-anterolateral thigh, can repeat every 3 to 5 minutes as needed. If signs of poor perfusion* are present or symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below)
Place patient in recumbent position, if tolerated, and elevate lower extremities
Oxygen: Give 6 to 8 liters per minute via face mask, or up to 100 percent oxygen as needed
Normal saline rapid bolus: Treat signs of poor perfusion* with rapid infusion of 20 mL per kilogram; re-evaluate and repeat fluid boluses (20 mL per kilogram) as needed; massive fluid shifts with severe loss of intravascular volume can occur; monitor urine output
Albuterol: For bronchospasm resistant to IM epinephrine, give albuterol 0.15 mg per kilogram (minimum dose: 2.5 mg) in 3 mL saline inhaled via nebulizer; repeat as needed
H1 antihistamine: Give diphenhydramine 1 to 2 mg per kilogram (max 50 mg) IV; can give IM if symptoms are less severe
H2 antihistamine: Consider giving ranitidine 1 to 2 mg per kilogram (max 50 mg) IV

Glucocorticoid: Consider giving methylprednisolone 2 mg per kilogram (max 125 mg) IV
Hemodynamic and pulse oximetry monitoring should be performed continuously
TREATMENT OF REFRACTORY SYMPTOMS
Epinephrine infusion: Patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion at 0.1 to 1 microgram per kilogram per minute, titrated to effect and with constant hemodynamic monitoring
Vasopressors: Patients may require large amounts of IV crystalloid to maintain blood pressure; if response to epinephrine and saline is inadequate, dopamine (5 to 20 micrograms per kilogram per minute) can be given as continuous infusion, titrated to effect and with constant hemodynamic monitoring

* See the topic "Assessment of perfusion in pediatric resuscitation".

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